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STUDIES ON C-NOR-D-HOMOSTEROIDS—IX

SOLVOLYSIS OF 14β-HYDROXY-12β-TOSYLOXYSTEROIDS[1]

Y. SHIMIZU and H. MITSUHASHI

Faculty of Pharmaceutical Sciences, Hokkaido University, Sapporo, Japan

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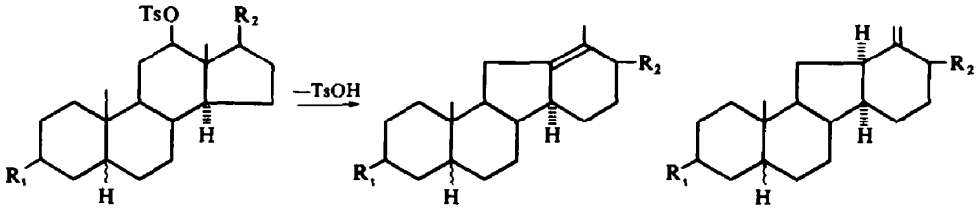
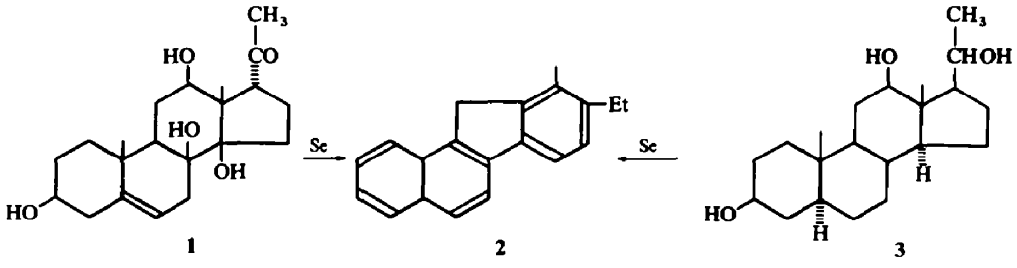
Abstract—The solvolysis of 14β-hydroxy-12β-tosyloxysteroids has been shown to afford C-nor-D-homosteroids with C/D-*trans* juncture.

THE solvolysis of 12β-tosyloxysteroids having the C/D-*trans* juncture affords C-nor-D-homosteroids with a double bond at $\Delta^{12(13)}$ (type A) and $\Delta^{13(18)}$ (type B).[2]

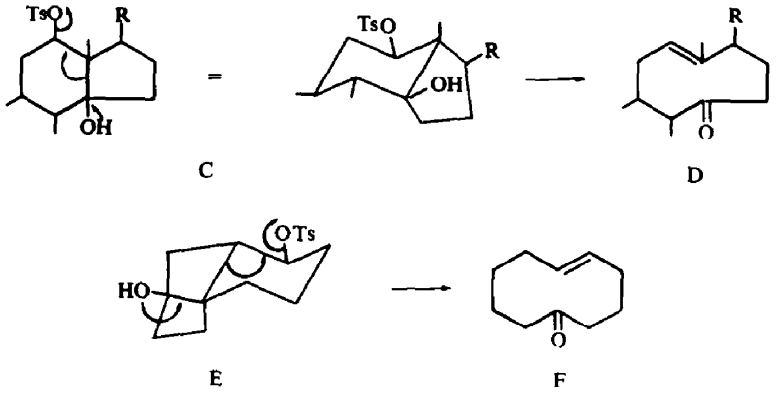


During the structural studies of polyhydroxypregnanes isolated from Asclepiadaceae family, the selenium dehydrogenation of compounds as represented by lineolon (**1**), which give Jacobs hydrocarbon (**2**) lead to the erroneous assignment of the skeleton structure.[3] As 3β,12β,20β-trihydroxypregnane (**3**) also gives **2** in excellent yield by selenium dehydrogenation, later the structures included the 12β,14β-dihydroxy moiety.[4] Since then, the authors have been interested in the solvolysis of 14β-hydroxy-12β-tosyloxysteroids.



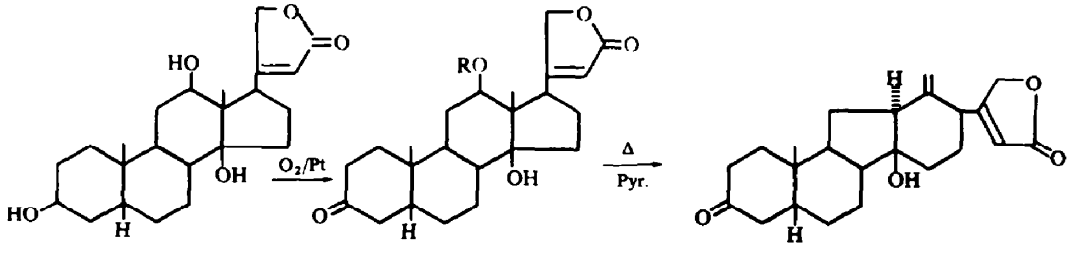
The solvolysis of 12β-tosyloxysteroids with a 14β-OH function has two peculiar aspects as compared with ordinary 14α-H-steroids. One is a completely different sterical environment created by the difference of the C/D juncture, which could disturb the C-nor-D-homo annulation. The other is the presence of an OH group

at the β-position which may induce fragmentation to a seco-product (D) rather than ring rearrangement. Usually, such a fragmentation is favoured by the antiparallel relation of the leaving group and the OH group. But, several examples like E, where the OH groups are in almost the same relation as those of 12β,14β-dihydroxy-steroids, are known to afford the fragmentation product of the type F.[5]



In order to examine these possibilities, the following experiments using digoxigenin (**4**) as the starting material were undertaken.

Digoxigenin (**4**) was selectively oxidized[6] to 3-dehydrodigoxigenin (**5**), m.p. 250–252° in a practically quantitative yield. Tosylation of **5** afforded the corresponding 12-tosylate (**6**) as an amorphous substance. Although all attempts to crystallize the tosylate failed, the uniformity of the product was confirmed by TLC and NMR. This tosylate was dissolved in pyridine and, this time, heated under reflux for 1 hr. The product isolated, m.p. 192–195°, was crystalline and homogenous with the molecular formula, $C_{23}H_{30}O_4$, showing the loss of one oxygen function. The IR spectrum shows the presence of an OH group at 3520 cm^{-1} besides the 3-ketone (1700 cm^{-1}) and butenolide moiety (1790, 1758, 1630 cm^{-1}). The NMR spectrum exhibits only one Me signal at τ 9·00, and the absence of a signal for a vinylic Me group exclude the possibility that the product is a type D compound. In the lower field, a pair of signals at τ 4·79 and 4·95 are typical for a terminal methylene group suggesting the Me group was converted to an exomethylene group, which is recognized by absorptions at 1658 and 910 cm^{-1} in the IR. The signals at τ 5·29 and 4·02 can be



4

5: R = H
6: R = Ts

7

assigned to the butenolide group and absence of other signals in this region suggests that the OH group observed in the IR spectrum can only exist as a tertiary alcohol. Based on these spectral data, we were able to conclude a C-nor-D-homo-rearranged structure, 7, and the signals at τ 6·52 can be assigned to the 17-hydrogen squeezed between two double bonds. The compound 7 is extremely labile to dehydration, thus treatment with thionyl chloride in cold pyridine afforded a black resinous material, from which no appreciable product was isolated. The mass spectrum of 7 is shown in Fig. 2 and its fragmentation pattern is also speculated as described.

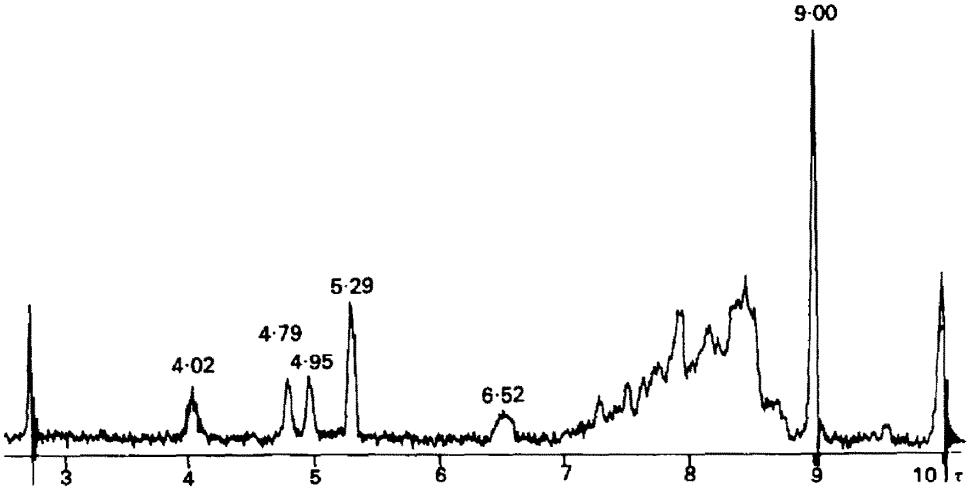


FIG. 1 NMR spectrum of the compound, 7.

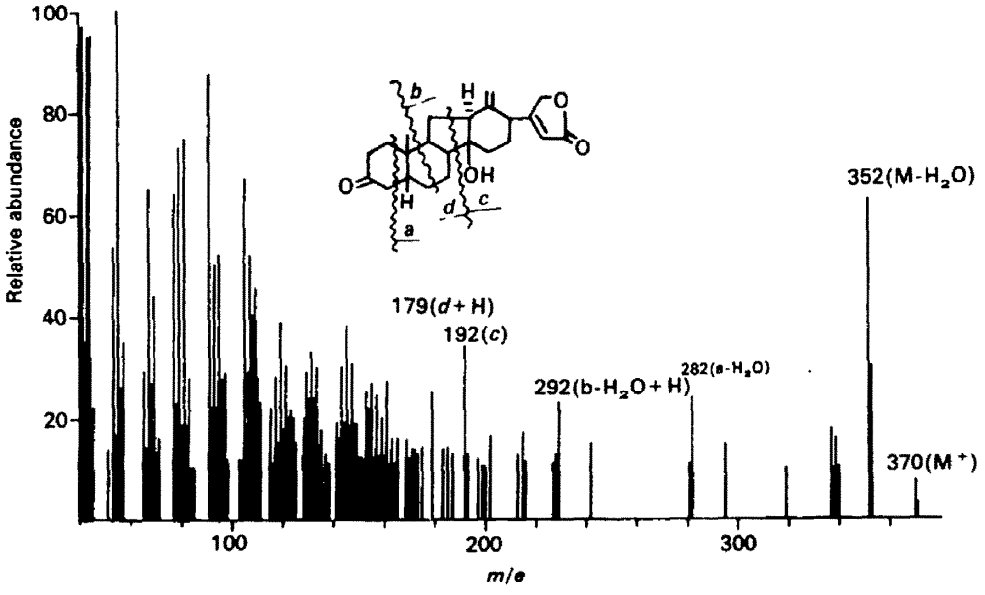
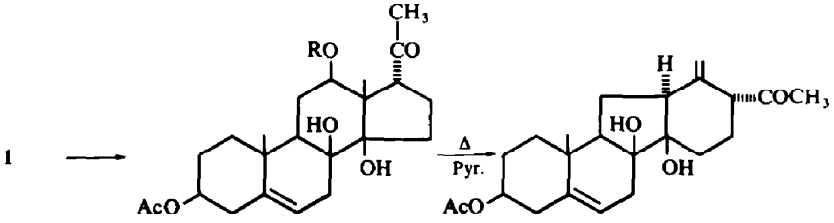


FIG 2 Mass spectrum of the compound, 7.

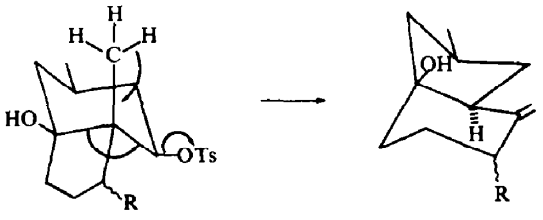
In an attempt to obtain more information on the rearrangement, lineolon (=deacylcynanchogenin; **1**)[7] was submitted to the same reaction. Lineolon was carefully acetylated under controlled conditions to the 3-monoacetate (**8**), m.p. 140–145°. The position of acetylation was confirmed as the 3-OH group in the NMR spectrum which has a quartet at τ 6·22 (J = 11 and 5·7) for the 12α-hydrogen and a multiplet at τ 5·39 for the 3α-hydrogen. Tosylation of **8** in pyridine at room temperature proceeds very slowly and under forced conditions dehydration of the tertiary OH functions occur. After prolonged treatment at room temperature, a mixture of the tosylate **9**, starting material and decomposed compounds was isolated. The mixture was heated in pyridin under reflux without isolation of the pure tosylate. Two crystalline products were isolated, one the recovered monoacetate (**8**), and the other the less polar substance, **10**, m.p. 162–167°. The overall yield of **10** was ca. 50% and the compound has the composition, $C_{23}H_{32}O_5$ and an IR spectrum showing the presence of a terminal methylene group at 1642 and 900 cm^{-1}. The NMR spectrum provided convincing evidence for the structure. Two acetyl signals were seen at τ 7·93 and 7·92 for a 3-acetate and C-21 Me group and only one angular Me signal appeared at τ 8·73, while a pair of signals at τ 5·00 and 5·22 confirm the formation of an exomethylene structure. Thus, as in the case of **7**, the compound has also a C-nor-D-homo-rearranged structure.



8: R = H
9: R = Ts

10

In connection with the stereochemistry, the rearrangement is expected to occur by a mechanism which involves the removal of the tosyloxy moiety, concomittant migration of the 13,14-bond and the abstraction of the C-18 hydrogen[2,8] as described



G H

in the following scheme (G → H), and, considering the mild condition for the solvolysis, all the configurations in the primary products are expected to be preserved. Thus, these products are the first examples of 12α,14β-C/D-*trans*-C-nor-D-homosteroids. In the rearrangement of C/D-*trans*-steroids, the products are of 12α,14α-C/D-*cis* type.[2,8]

EXPERIMENTAL

All m.ps were measured on a Kofler block and corrected. IR spectra were taken on a Shimadzu instrument type-IR. NMR data were obtained by a Hitachi instrument working at 60 mc.

Digoxigenin (**4**) was obtained by hydrolysis of digoxin (Sandoz A.G.) according to the procedure by Smith.[9]

3-Dehydrodigoxigenin (**5**). This compound was prepared basically by Tamm and Gubler's procedure,[6] but the following modification gave the more satisfactory result.

$PtO_2 \cdot H_2O$ (100 mg) in 10 ml water was reduced with H_2 for 1 hr. After removal of H_2, oxygen was introduced and the catalyst was shaken for 15 min. The catalyst was collected by filtration and added to a soln of **4** (500 mg) in acetone (40 ml) and water (10 ml), and swirled vigorously in an O_2 atm. After 7 hr, complete disappearance of the starting material was observed. Catalyst was removed by filtration and the content was reduced to a small volume. The separated crystals were collected and recrystallized from acetone–water to needles, m.p. 250–251° (reported[6]: m.p. 248–258°).

3-Dehydrodigoxigenin tosylate (**6**). Compound **5** (500 mg) was dissolved in pyridine (5 ml) and tosyl chloride (300 mg) was added. The soln was left at room temp for 24 hr. Dilution with water and extraction with ether followed by a usual procedure gave an amorphous **6**, which failed to crystallize but displayed a single spot on TLC and a uniform NMR spectrum. ν_{max}^{film} 1780, 1750, 1700 and 1630 cm^{-1} τ (in $CDCl_3$) 9·12 (s, 3H, 19-Me), 9·02 (s, 3H, 18-Me), 7·52 (s, 3H, aromatic Me), 5·63 (qu, 1H, 12α-H), 5·24 (s, 2H, 21-CH_2), 6·21 (—C=CHCO—), 2·21, 2·63 (AB system, J = 9 c/s, aromatic hydrogens).

C-Nor-D-homocardenolide derivative (**7**). A soln of the tosylate (100 mg) in anhyd pyridine (1 ml) was heated at reflux for 1 hr. The soln was tested by NMR *in situ*. The spectrum shows only one Me signal at τ 9·13, besides the Me signal of the disbanded *p*-toluenesulfonic acid. The soln was diluted with water and separated crystals were collected by filtration. Recrystallization from CH_2Cl_2 and isopropyl ether gave fine plates of **7**, m.p. 192–195°; λ_{max}^{EtOH} 217 mμ(10,200), ν_{max}^{Nujol} 3520, 1790, 1758, 1700, 1658, 1630 and 910 cm^{-1}; NMR (*vide supra*). (Found: C, 74·56; H, 8·02. $C_{23}H_{30}O_4$ requires: C, 74·56; H, 8·16%). High resolution mass spectroscopy also gave $C_{23}H_{30}O_4$.

Lineolon-3-mono-acetate (**8**). Lineolon (100 mg) was dissolved in a mixture of pyridine (2 ml) and Ac_2O (0·1 ml) and left at 15° for 15 hr. The soln was diluted with water and extracted with ether. The extract was processed by usual method. Chromatography of the product over alumina by elution with CH_2Cl_2–MeOH (99:1) gave **8** (55 mg). Recrystallization from ether afforded prisms, m.p. 140–145°, ν_{max}^{Nujol} 3500, 1740, 1690 and 1250 cm^{-1}; τ (in $CDCl_3$) 8·80 (s, 6H, 21-Me and acetate), 6·56 (tr, 1H, 17-H), 6·22 (qu, 1H, 12-H), 5·39 (broad m, 1H, 3-H) and 4·62 (tr, 1H, 6-H). (Found: C, 67·80; H, 8·23. $C_{23}H_{34}O_6$ requires: C, 67·95; H, 8·43%).

C-Nor-D-homo-derivative (**10**). A soln of the above acetate (50 mg) and tosyl chloride (50 mg) in anhyd pyridine (1 ml) was allowed to stand at 28° for 4 days. The mixture was poured into ice-water and extracted with ether. After usual procedure the extract gave a resinous residue, which was dissolved in 1 ml of pyridine and heated at reflux for 1 hr. The soln was diluted with ether and washed with dil HCl and water successively. Removal of ether gave a glassy residue, which was submitted to a preparative TLC (silica gel HF_{254}, $CHCl_3$:EtOAc 1:3). Two major zones were extracted. The less mobile fraction gave 12 mg of **8**. The more mobile fraction (21 mg) was recrystallized from CH_2Cl_2–isopropyl ether as prisms (**10**), m.p. 162–167°, ν_{max}^{Nujol} 3550, 1728, 1700, 1642, 900 cm^{-1}; τ (in $CDCl_3$) 8·73 (s, 3H, 19-Me), 7·93, 7·92 (each s, 3H, 21-Me and acetate), 5·00, 5·22 (each s, 1H, terminal methylene) and 4·55 (m, 1H, 6-H); ε_{214} mμ ca. 6000. (Found: C, 71·40; H, 8·28. $C_{23}H_{32}O_5$ requires: C, 71·10; H, 8·30%).

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